REMARKS

1. **According to p8 last paragraph of the 37 CFR 1.132 declaration of 10/27/2008 it is indicated that compound 10 was prepared in two ways: the manner of Ma et al giving a 6:4 epimer mixture and by reduction of compound 13 giving a 1:7 epimer mixture. It is also indicated that said epimers may be separated by flash chromatography. In this vein, what sample was used in the TOCSY, MS and HPLC experiments set forth on pp9-14 of said declaration: the 6:4 mixture prepared in the manner of Ma et al; the 1:7 mixture prepared by reduction of compound 13; or a flash purified epimer?**

The 6:4 mixture of epimers prepared in the manner of Ma et al, compound number 10, is identified as PCM425. The flash purified major isomer from the Ma synthesis route, compound number 10a, was isolated as PCM425f7 and PCM425f8, with the flash purified minor isomer from the Ma synthesis route, compound number 10b, isolated as PCM425f9-10 and PCM425f11-13. Compound 10b was also obtained as the flash purified major isomer from the reduction of compound 13, isolated as various fractions of PCM402.

P9 Figure 1: the TOCSY spectrum of compound 10a was prepared using PCM425f7, the flash purified major isomer from the Ma synthesis route.

P9 Table 1: the chemical shifts in Table 1 of compound 10a were based on the two conformers of PCM425f7, the flash purified major isomer from the Ma synthesis route.

P11 Table 2: the mass spectrum tabulated in Table 2 of Compound 10 was obtained with purified 10a, the flash purified major isomer from the Ma synthesis route.

P12 Table 3: the factorial experiments in Table 3 were conducted on the 6:4 mixture of epimers prepared in the manner of Ma et al, other than the second reaction (PCM427), which was conducted on compound 10a, the flash purified major isomer from the Ma synthesis route.

P14 Table + Figure 5: the HPLC chromatogram in Figure 5B is of compound 10a (PCM425f7), the flash purified major isomer from the Ma synthesis route. Retention times of both compound 10a (PCM425f7), the flash purified major isomer from the Ma synthesis route, and 10b (PCM402), the flash purified major isomer from the reduction of compound 13, are listed in the Table.

2. **If said TOCSY, MS and HPLC experiments were performed with one purified epimer, did the other epimer give the same results?**

P9 Figure 1: the TOCSY spectrum of the other purified epimer 10b was not obtained.

P9 Table 1: 1H NMR of the other purified epimer 10b was obtained, gave different result.

P11 Table 2: The mass spectra of crude Compound 10 and both purified epimers Compound 10a (prepared by Ma procedure) and 10b (prepared by Ma procedure and by reduction of Compound 13) were obtained, and gave similar results.

P12 Table 3: purified epimer 10a was employed in one experiment. Purified epimer 10b was not used.

P14 Table + Figure 5: HPLC data was obtained for both purified epimers, and gave different retention times.

In summary, in a number of the experiments, the other purified epimer was not used. In those experiments where the other purified epimer was used, it gave different results, other than mass spectra.

3. **What sample is injected in and what wavelength was used in each of the chromatograms set forth on pp 98-115 of the 37 CFR1.132 declaration of 10/27/2005?**
Note – should be 10/27/2008

Wavelengths are indicated in the text at the top left of each chromatogram, Sig=xxx. Sample identification is in brackets at the end of the text.

P99 top: wavelength = 220 nm; sample = PCM432F11 = purified aziridine 3a formed from factorial experiment of crude 10a prepared by Ma procedure.

P99 bottom: wavelength = 220 nm; sample = PCM425F8 = purified alcohol 10a prepared by Ma procedure.

P100 top: wavelength = 220 nm; sample = PCM416F21 = purified authentic compound 2 prepared via Compound 13.

P100 bottom: wavelength = 220 nm; sample = PCM430 = crude factorial experiment PCM430 showing triphenylphosphine oxide (6.377), aziridine **3a/3b** (6.948) and alcohol **10a/10b** (8.057).

P101 top: wavelength = 220 nm; sample = PCM429 = crude factorial experiment PCM 429 showing triphenylphosphine oxide (6.373) and aziridine 3 (6.940).

P101 bottom: wavelength = 220 nm; sample = coinjection of PCM416F21 (purified authentic compound 2) and PCM429 (crude factorial experiment PCM429) showing no change in retention time of compound 2 (8.707, vs 8.711) in presence of other reactants/products.

P103 top: wavelength = 220 nm; sample = PCM414 = crude factorial experiment PCM414.

P103 bottom: wavelength = 220 nm; sample = PCM416F21 = purified authentic compound 2 prepared via Compound 13.

P104 top; wavelength = 220 nm; sample = PCM429 = crude factorial experiment PCM429.

P104 bottom: wavelength = 252 nm; sample = PCM429 = crude factorial experiment PCM.

P106 top: wavelength = 220 nm; sample = coinjection of PCM429 (crude factorial experiment PCM429) with PCM416 (purified authentic compound 2 prepared via Compound 13).

P106 bottom: wavelength = 220 nm; sample = PCM429 = crude factorial experiment PCM429.

P107 top: wavelength = 220 nm; sample = PM420 = crude factorial experiment PCM430.

P107 bottom: wavelength = 252 nm; sample = PCM430 = crude factorial experiment PCM430.

P108 top: wavelength = 220 nm; sample = PCM431 = crude factorial experiment PCM431.

P108 bottom: wavelength = 220 nm; sample = PCM4167F21 = purified authentic compound 2 prepared via Compound 13.

P109 top: wavelength = 220 nm; sample = PCM432 = crude factorial experiment PCM432.

P109 bottom: wavelength = 252 nm; sample = PCM432 = crude factorial experiment PCM432.

P110: expansion/overlay of chromatograms from p109 sample PCM432 (crude factorial experiment PCM432); top trace wavelength = 252 nm, bottom trace wavelength = 220 nm.

P111 top: wavelength = 220 nm; sample = PCM433 = crude factorial experiment PCM433.

P111 bottom: wavelength = 252 nm; sample = PCM 433 = crude factorial experiment PCM 433.

P112 top: wavelength = 220 nm; sample = PCM434 = crude factorial experiment PCM434.

P112 bottom: wavelength = 252 nm; sample = PCM434 = crude factorial experiment PCM434.

P113 top: wavelength = 220 nm; sample = PCM435 = crude factorial experiment PCM435.

P113 bottom: wavelength = 252 nm; sample = PCM435 = crude factorial experiment PCM 435.

P114 top: wavelength = 220 nm; sample = PCM427 = crude factorial experiment PCM427.

P114 bottom: wavelength = 252 nm; sample = PCM427 = crude factorial experiment PCM427.

P115 top: wavelength = 220 nm; sample = PCM428 = crude factorial experiment PCM428.

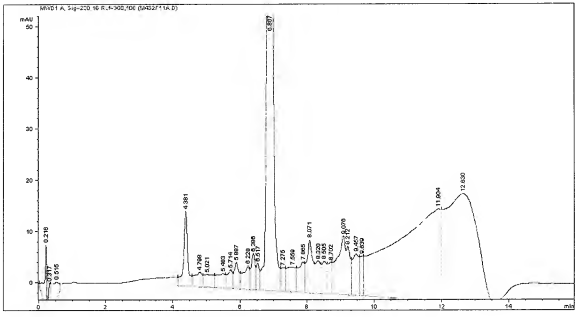
P115 bottom: wavelength = 252 nm; sample = PCM428 = crude factorial experiment PCM428.

In relation to the above the applicants note that authentic compound 2 was identified as PCM416F21 and is shown on the top spectrum of page 100 which was an injection of the purified compound and can also be seen in the bottom spectrum of page 101 which is a coinjection of purified compound 2 and crude factorial experiment PCM429. As stated above the purified authentic compound when injected as shown on the top chromatogram on page 100 and on the bottom chromatogram of page 101 demonstrated no change in retention time irrespective of whether it was a pure or a coinjection.

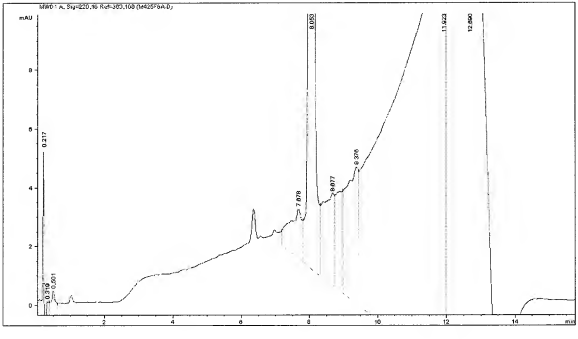
4. What is the retention time of the smaller peaks in the chromatograms set forth on pp 98-15 of the 37 CFR 1.132 declaration of 10/27/2005? ***Note – should be 10/27/2008***

Please find vertically expanded chromatograms with retention times of smaller peaks marked. For some chromatograms, sloping baselines made peak picking difficult. The expansions of the combinatorial reaction products indicate no sign of authentic cyclic material 2 at its retention time of 8.711 (purified 2) / 8.707 (coinjection of 2 with reaction mixture) minutes.

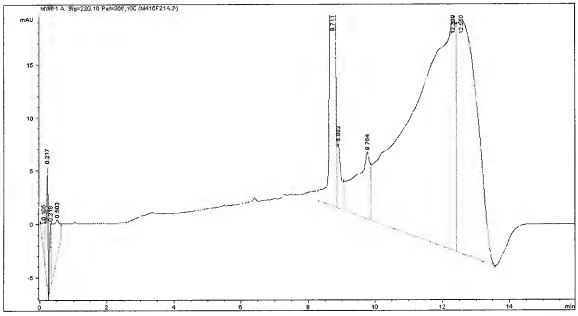
p99 top: wavelength = 220 nm; sample = PCM432F11



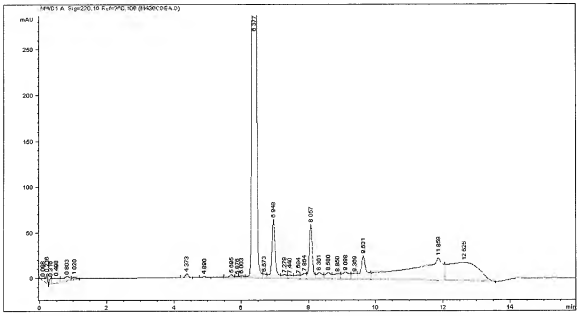
p99 bottom: wavelength = 220 nm; sample = PCM425F8



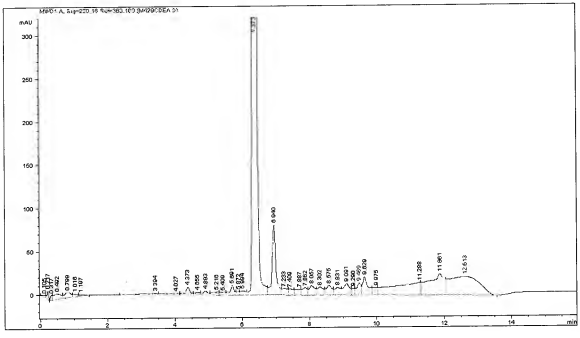
p100 top: wavelength = 220 nm; sample = PCM416F21



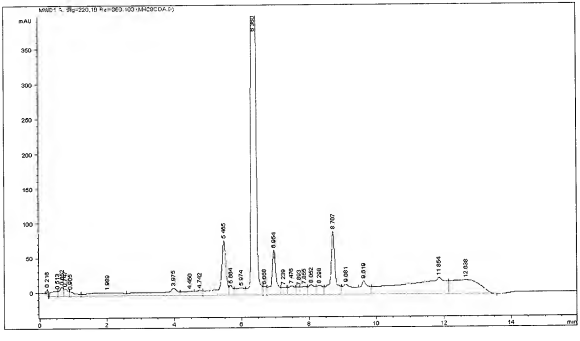
p100 bottom: wavelength = 220 nm; sample = PCM430



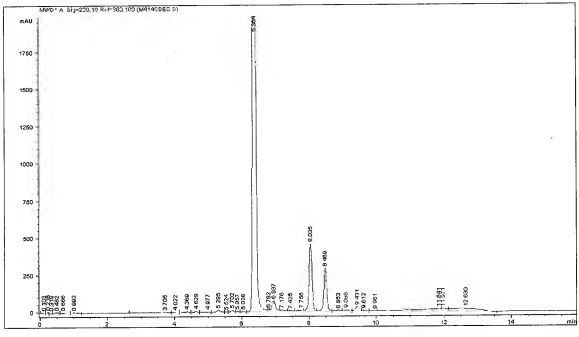
p101 top: wavelength = 220 nm; sample = PCM429



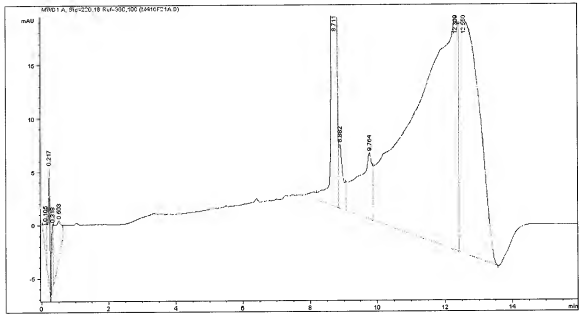
p101 bottom: wavelength = 220 nm; sample = coinjection of PCM416F21 and PCM429



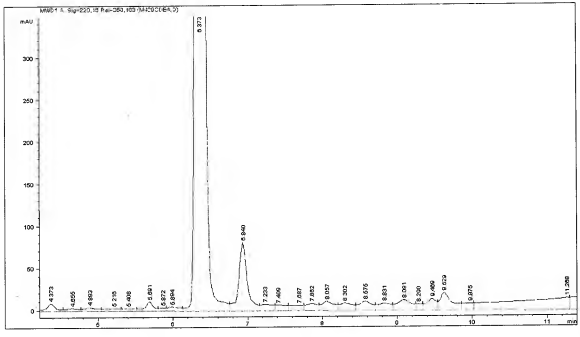
p103 top: wavelength = 220 nm; sample = PCM414



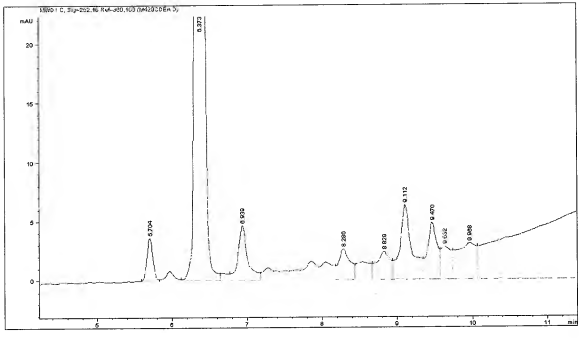
p103 bottom: wavelength = 220 nm; sample = PCM416F21



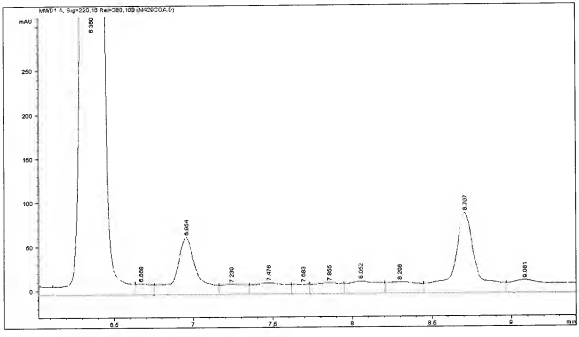
p104 top: wavelength = 220 nm; sample = PCM429



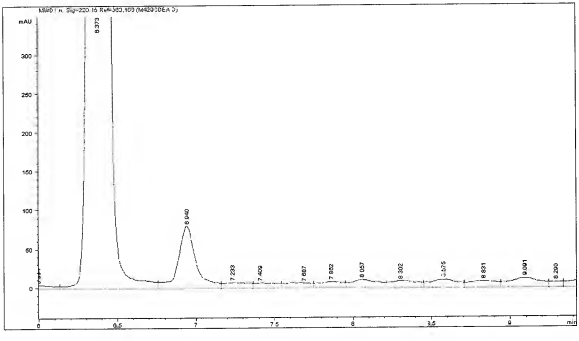
p104 bottom: wavelength = 252 nm; sample = PCM429



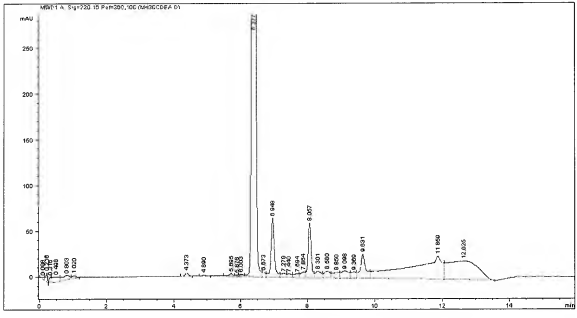
p106 top: wavelength = 220 nm; sample = coinjection of PCM429 with PCM416



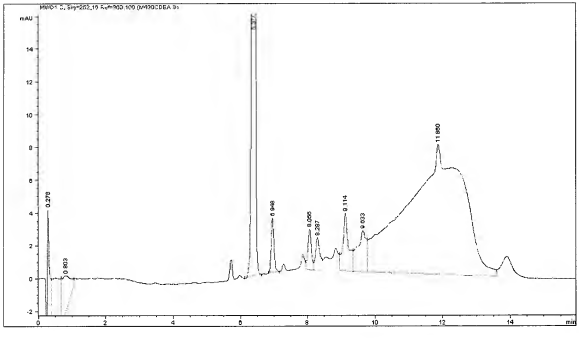
p106 bottom: wavelength = 220 nm; sample = PCM429



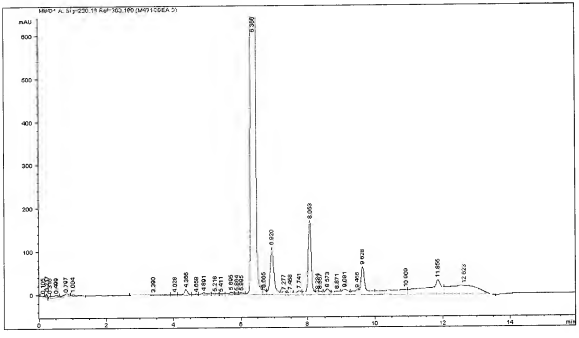
p107 top: wavelength = 220 nm; sample = PCM430



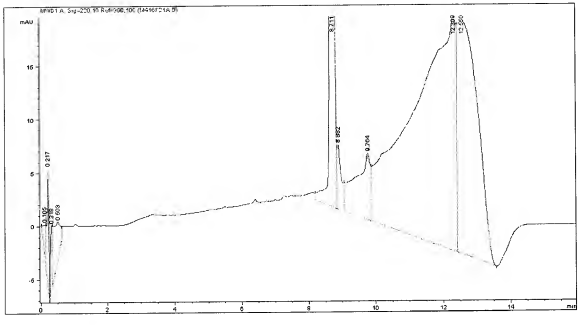
p107 bottom: wavelength = 252 nm; sample = PCM430



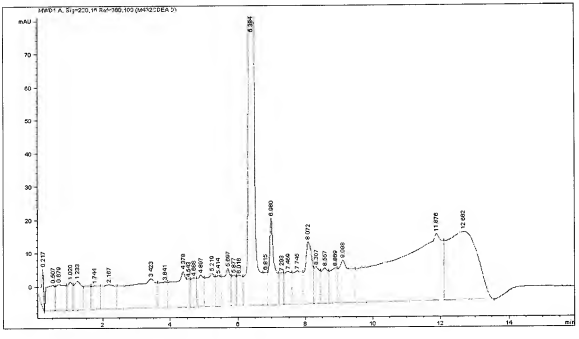
p108 top: wavelength = 220 nm; sample = PCM431



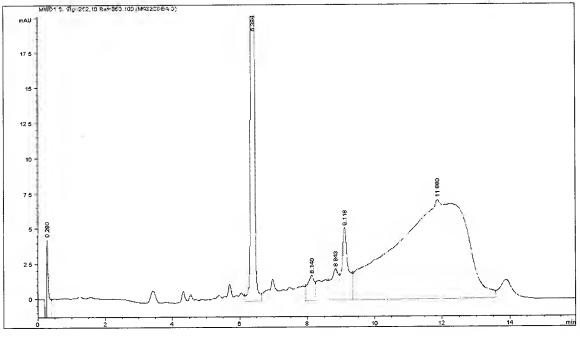
p108 bottom: wavelength = 220 nm; sample = PCM416F21



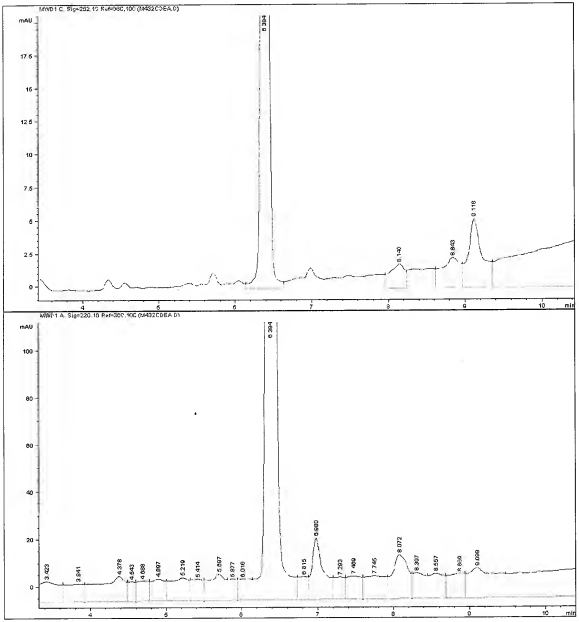
p109 top: wavelength = 220 nm; sample = PCM432



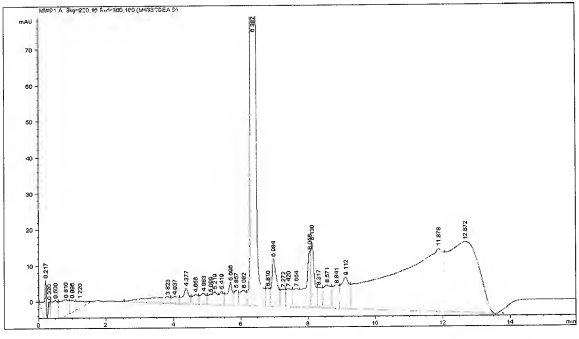
p109 bottom: wavelength = 252 nm; sample = PCM432



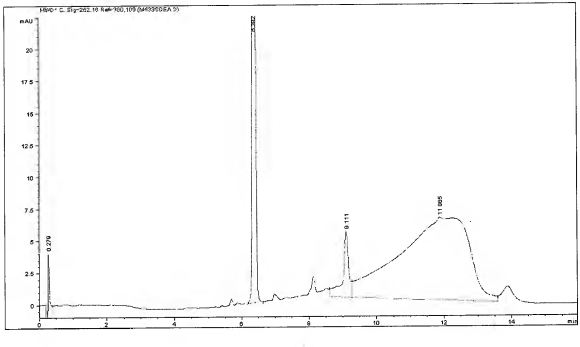
p110: expansion/overlay of chromatograms from p109 sample PCM 432 (crude factorial experiment PCM432); top trace wavelength = 252 nm, bottom trace wavelength = 220 nm



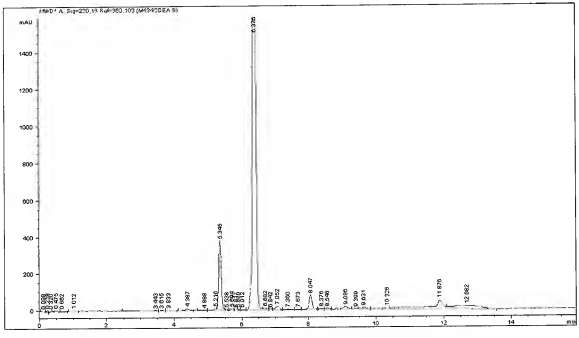
p111 top: wavelength = 220 nm; sample = PCM433



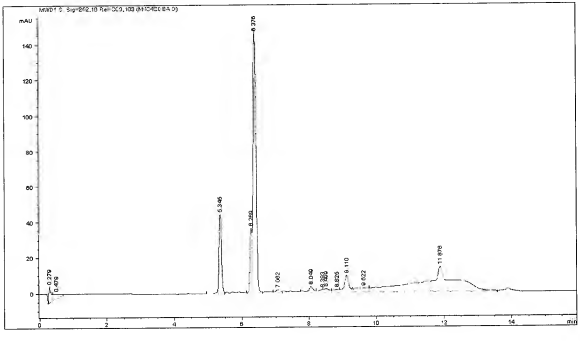
p111 bottom: wavelength = 252 nm; sample = PCM433



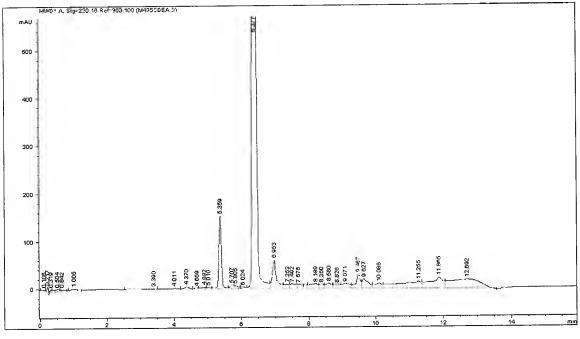
p112 top: wavelength = 220 nm; sample = PCM434



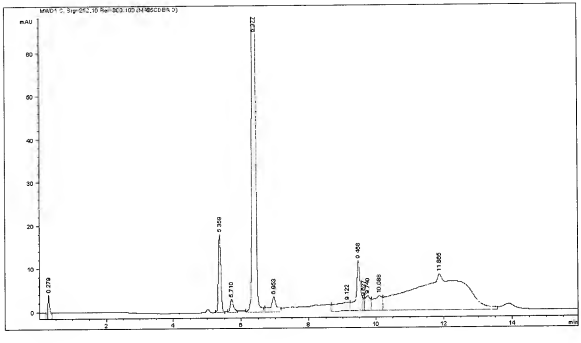
p112 bottom: wavelength = 252 nm; sample = PCM434



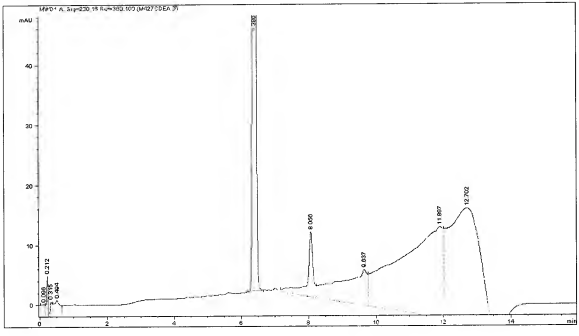
p113 top: wavelength = 220 nm; sample = PCM435



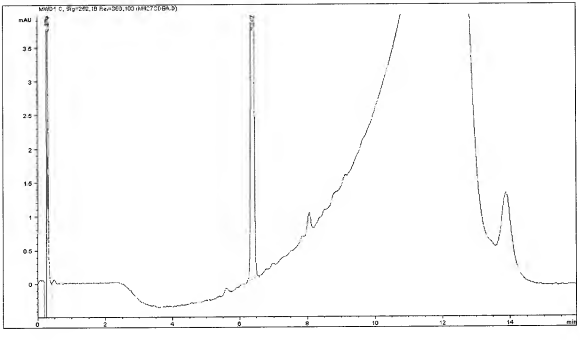
p113 bottom: wavelength = 252 nm; sample = PCM435



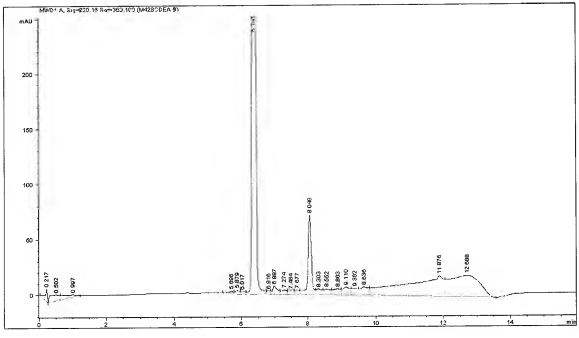
p114 top: wavelength = 220 nm; sample = PCM427



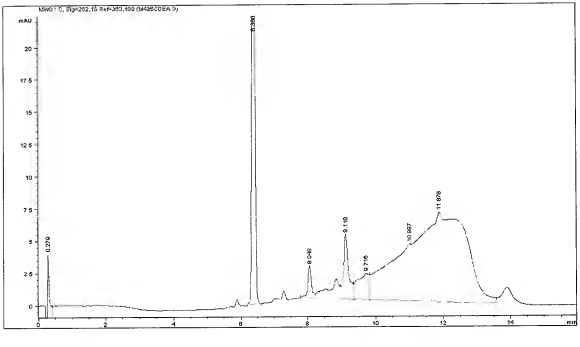
p114 bottom: wavelength = 252 nm; sample = PCM427



p115 top: wavelength = 220 nm; sample = PCM428



p115 bottom: wavelength = 252 nm; sample = PCM428



Whilst the applicants submit that the expanded chromatograms provide the answers, in order to assist the examiner the applicants have tabulated the retention times from these chromatograms.

CHROMATOGRAPH	**PEAK RETENTION TIMES**
P99 top Sample = PCM432F11	0.216, 0.317, 0.515, 4.381, 4.798, 5.021, 5.483, 5.714, 5.887, 6.229, 6.386, 6.517, 6.867, 7.275, 7.559, 7.865, 8.071, 8.320, 8.505, 8.702, 9.076, 9.212, 9.457, 9.637, 11.904, 12.630
P99 bottom Sample = PCM425F8	0.217, 0.319, 0.501, 7.679, 8.053, 8.677, 9.376, 11.923, 12.690
P100 top Sample = PCM416F21	0.105, 0.217, 0.318, 0.503, 8.711, 8.882, 9.764, 12.309, 12.550
P100 bottom Sample = PCM430	0.098, 0.216, 0.316, 0.498, 0.803, 1.020, 4.373, 4.890, 5.695, 5.876, 6.003, 6.377, 6.673, 6.948, 7.279, 7.440, 7.694, 7.864, 8.057, 8.301, 8.580, 8.850, 9.098, 9.369, 9.631, 11.859, 12.625
P101 top Sample = PCM429	0.105, 0.217, 0.317, 0.492, 0.799, 1.016. 1.197, 3.394, 4.027, 4.373, 4.655, 4.893, 5.216, 5.409, 5.691, 5.872, 5.994, 6.373, 6.940, 7.233, 7.409, 70687, 7.862, 8.057, 8.302, 8.575, 8.831, 9.091, 9.290, 9.469, 9.629, 9.975, 11.268, 11.861, 12.613
P101 bottom Sample = PCM416F21 and PCM429	0.216, 0.513, 0.652, 0.747, 0.906, 1.989, 3.975, 4.450, 4.742, 5.465, 5.664, 5.974, 6.360, 6.668, 6.954, 7.239, 7.476, 7.693, 7.855, 8.052, 8.298, 8.707, 9.081, 9.619, 11.854, 12.638
P103 top Sample = PCM414	0.103, 0.216, 0.319, 0.482, 0.666, 0.993, 3.705, 4.022, 4.369, 4.628, 4.977, 5.285, 5.524, 5.702, 5.857, 6.028, 6.364, 6.782, 6.937, 7.176, 7.426, 7.756, 8.035, 8.469, 8.863, 9.086, 9.431, 9.612, 9.961, 11.841, 11.971, 12.630
P103 bottom Sample = PCM416F21	0.105, 0.217, 0.318, 0.503, 8.711, 8.882, 9.764, 12.369, 12.550
P104 top Sample = PCM429	4.373, 4.655, 4.893, 5.216, 5.409, 5.691, 5.872, 5.994, 6.373. 6.940, 7.233, 7.409, 7.687, 7.862, 8.057, 8.302, 8.575, 8.831, 9.091, 9.290, 9.469, 9.629, 9.975, 11.268
P104 bottom Sample = PCM429	5.704, 6.373, 6.939, 8.286, 8.829, 9.112, 9.479, 9.632, 9.968
P106 top Sample = coinjection of PCM429 with PCM416	6.360, 6.668, 6.954, 7.239, 7.476, 7.693, 7.855, 8.052, 9.298, 8.707, 9.081
P106 bottom Sample = PCM429	6.373, 6.940, 7.233, 7.409, 7.687, 7.862, 8.057, 8.302, 8.575, 8.831, 9.091, 9.290
P107 top	0.098, 0.216, 0.316, 0.498, 0.803, 1.020, 4.373, 4.890,

CHROMATOGRAPH	PEAK RETENTION TIMES
Sample = PCM430	5.695, 5.876, 6.003, 6.377, 6.673, 6.948, 7.279, 7.440, 7.694, 7.864, 8.057, 8.301, 8.580, 8.850, 9.098, 9.369, 9.631, 11.859, 12.625
P107 bottom Sample = PCM430	0.278, 0.803, 6.377, 6.948, 8.056, 8.287, 9.114, 9.633, 11.680
P108 top Sample = PCM431	0.105, 0.217, 0.316, 0.499, 0.797, 1.004, 3.390, 4.028, 4.366, 4.659, 4.891, 5.216, 5.411, 5.695, 5.864, 5.995, 6.366, 6.665, 8.920, 7.277, 7.458, 7.741, 8.053, 8.284, 8.357, 8.573, 8.871, 9.091, 4.466, 9.628, 10.909, 11.855, 12.623
P108 bottom Sample = PCM416F21	0.105, 0.217, 0.318, 0.503, 8.711, 8.882, 9.764, 12.369, 12.550
P109 top Sample = PCM432	0.217, 0.507, 0.679, 1.020, 1.233, 1.744, 2.167, 3.423, 3.841, 4.378, 4.543, 4.688, 4.897, 5.219, 5.414, 5.697, 5.877, 6.016, 6.384, 6.815, 6.980, 7.293, 7.469, 7.745, 8.072, 8.307, 8.557, 8.869, 9098, 11.876, 12.662
P109 bottom Sample = PCM432	0.280, 6.384, 8.140, 8.843, 9.118, 11.880
P110: expansion/overlay of chromatograms from p109 sample PCM432	6.384, 8.140, 8.843, 9.118 3.423, 3.841, 4.378, 4.543, 4.688, 4.897, 5.219, 5.414, 5.697, 5.877, 6.016, 6.384, 6.815, 6.980, 7.293, 7.469, 7.745, 8.072, 8.307, 8.557, 8.869, 9.098
P111 top Sample = PCM433	0.217, 0.320, 0.500, 0.810, 0.996, 1.220, 3.823, 4.037, 4.377, 4.656, 4.883, 5.099, 5.219, 5.419, 5.696, 5.857, 6.082, 6.382, 6.810, 6.984, 7.272, 7.420, 7.664, 8.056, 8.130, 8.713, 8.571, 8.841, 9.112, 11.878, 12.672
P101 bottom Sample = PCM433	0.279, 6.382, 9.111, 11.885
P112 top Sample = PCM434	0.098, 0.218, 0.320, 0.475, 0.662, 1.012, 3.443, 3.615, 3.833, 4.387, 4.888, 5.216, 5.345, 5.538, 5.694, 5.817, 5.880, 6.012, 6.376, 6.682, 6.842, 7.052, 7.360, 7.673, 8.047, 8.376, 8.546, 9.086, 9.399, 9.631, 10.362, 11.876, 12.682
P112 bottom Sample = PCM434	0.279, 0.479, 5.345, 6.268, 6.376, 7.062, 8.049, 8.393, 8.499, 8.825, 9.110, 9.622, 11.876
P113 top Sample = PCM435	0.106, 0.217, 0.319, 0.504, 0.642, 1.005, 3.390, 4.011, 4.370, 4.669, 4.892, 5.010, 5.359, 5.707, 5.805, 6.024, 6.377, 6.953, 7.353, 7.492, 7.676, 8.189, 8.360, 8.580, 8.826, 9.071, 9.467, 9.627, 10.086, 11.255, 11.865, 12.692
P113 bottom Sample = PCM435	0.279, 5.359, 5.710, 6.377, 6.953, 9.122, 9.468, 9.627, 9.740, 10.088, 11.865
P114 top	0.096, 0.212, 0.315, 0.494, 6.386, 8.056, 9.637, 11.897,

CHROMATOGRAPH	PEAK RETENTION TIMES
Sample = PCM427	12.702
P114 bottom Sample = PCM427	0.279, 6.387
P115 top Sample = PCM428	0.217, 0.502, 0.997, 5.696, 5.879, 6.017, 6.380, 6.816, 6.987, 7.274, 7.484, 7.677, 8.048, 8.303, 8.552, 8.863, 9.110, 9.362, 9.636, 11.876, 12.688
P115 bottom Sample = PCM428	0.279, 6.380, 8.048, 9.110, 9.716, 10.997, 11.878

As can be seen the only chromatographs that contain a peak at the relevant line of authentic 2 (at 8.707-8.711) of any significance were that of pure sample 2 (page 100 top, 103 bottom and 108 bottom) and the coinjections of pure sample 2 (page 101 bottom and 106 top).

CONCLUSION

The Examiner is invited to telephone Applicants' attorney at (612) 373-6941 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

espectfully submitted,

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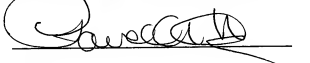
Date: April 7, 2009

By 
Geoffrey K. Cooper
Reg. No. 51,266

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 7th day of April 2009.

PATRICIA A. HULTMAN

Name



Signature